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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,259	07/09/2004	Shunichi Shiozawa	61646 (70904)	7532

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
12/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,259	SHIOZAWA ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/15/2008 has been entered.

Response to Amendment

2. The declaration under 37 CFR 1.132 filed 8/14/2008 is sufficient to overcome the 102 (a) rejection of claim 4 based upon Shiozawa. As the declaration states the invention is not by others.

Claim Status

Claims 4 and 11 are pending.

The 102 rejection based on Shiozawa has been withdrawn as noted above.

The 102 rejection of Davis has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection has been modified in view of the amendment to claim 4.

These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claim 4 encompasses a method of evaluating the possibility of onset or onset of rheumatoid arthritis (RA) in a human subject, by detecting whether a gene coding a protein comprising the amino acid sequence of SEQ ID NO 1 is homozygously present in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject: wherein the step of evaluating comprise determining the possibility of onset of rheumatoid arthritis is increased if the gene is present homozygously in the subject.

Thus the claims broadly encompass evaluating the onset of RA by the determining whether the homozygous presence of "any" nucleic acid that would result in a protein comprising the amino acid sequences of SEQ ID NO 1 is present in a subject and if it is homozygously expressed there is an increased possibility of RA.

Claim 11 draws the invention to wherein the rheumatoid arthritis is sporadic rheumatoid arthritis.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches the insertion of GGT at positions 805-807 resulting in a glycine being inserted into amino acid position 269 of SEQ ID NO.1 (see page 25, 1st full paragraph). The specification further teaches this insertion is depicted in SEQ ID NO. 2 (see page 25, line 10). The specification teaches a 3 base deletion (see page 10, line 11).

The specification in figure 4 teaches that 1 subject of the 69 assayed with familial RA were homozygous for the presence of a gene encoding the protein of SEQ ID NO 1 (homozygous insertion). The specification teaches that none of the 28 relatives to subjects with familial RA were homozygous for the gene encoding the protein of SEQ ID NO 1.

The specification in figure 4 teaches that 4 subject of the 225 subjects assayed with sporadic RA were homozygous for the presence of a gene encoding the protein of SEQ ID NO 1(homozygous insertion). The specification teaches that none of the 383 relatives to subjects with sporadic RA had homozygous insertion.

The specification teaches of 1410 alleles examined, 1296 were not SEQ ID NO1 and 114 were SEQ ID NO1. This suggests that SEQ ID NO 1 is an underrepresented allele in the population studied.

The state of prior art and the predictability or unpredictability of the art:

Applicants have provided the Declaration under 37 CFR 1.132 filed September 11, 2007 by the inventor. The declaration teaches a study performing RT-PCR from RNA isolated from whole blood and healthy subjects to obtain a partial sequence of Angiopoitien-1 (paragraph 4). The declaration further teaches the PCR product was sequenced. The Declaration teaches 115 patients with sporadic RA were assayed and 85 controls. The declaration teaches 33 sporadic subjects with the homozygous for the insertion, while 15 of the control subjects were homozygous. The declaration teaches there is a significant ($p=0.07$) trend toward the homozygous presence of the patients with sporadic RA.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn teaches 8 genes that have been associated with RA in table 1, among more than 166 genes that have been associated with disease.

Hirschhorn teaches that Table 3 teaches all studies that have been reproduced from those analyzed in table 1. Table 3 does not mention RA and thus suggests that the prior art gene association studies of RA are not reproducible. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (a) (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Post-filing art of Ioannidis (b) (PLOS Med Volume 2, issue 8, e 124, pages e0696-00701) teaches, "that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p-value less than 0.05. Research is not most appropriately represented and summarized by p-values, but, unfortunately, there is a widespread notion that medical research articles should be interpreted based only on p-values" (page 1, 2nd column). Ioannidis (b) teaches studies with small sample size (less than several thousand) are associated with lesser power and less likely reproducibility

(e0697), third column, 1st full paragraph). Ioannidis (b) teaches that financial interest of investigators allows for bias and prejudices outcomes (0698, 2nd column). Ioannidis (b) teaches the smaller the effect the lesser the portion of true findings is decreased (e697-thir column-top e698). Ioannidis (b) concludes that, "Most research findings are false for most research designs and for most fields" (page 699, 2nd column).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed the skilled artisan would first have to if determine a gene homozygously coding for a protein comprising the amino acids of SEQ ID No 1 is predictably (statistically) associated with RA or sporadic RA. The specification teaches that the homozygous insertion resulting in the protein of SEQ ID NO 1 occurs in 0.7% of 705 subjects examined, all of which had familial RA or sporadic RA. The declaration teaches of 200 subject examined 48 (24%) of the subject had the homozygous insertion. The declaration further teaches that of the 48 subjects with the homozygous insertion 15 were control subjects without RA. The declaration teaches that there was a trend (p value =0.07) toward the presence of homozygous insertion being present. However the pre-filing art of Hirschhorn and Ioannidis (a) teach that association of mutations with disease is unpredictable. Hirschhorn specifically analysis prior art relating to RA and finds none of the genetic RA associations previously found were replicated. Further the post filing art of Ioannidis (b) teaches, "Most research

findings are false for most research designs and for most fields" (page 699, 2nd column). Ioannidis (b) further teaches that large sample size (thousands) with p values of less that 0.05 teachings are the starting points for suggesting predictability of association studies. Thus in view of the unpredictability of association studies as taught by Hirschhorn and Ioannidis (a), as well as the specific teachings of Hirschhorn demonstrating that previous association with RA were not reproducible, it would be unpredictable to practice the invention as claimed based on the studies of the specification and declaration in which no statistical ($p<0.05$) association found. Further the post filing art of Ioannidis (b) teaches that association studies are "Most research findings are false for most research designs and for most fields" (page 699, 2nd column). Further, Ioannidis (b) suggests that studies with less than thousands of subjects, or with small effects ($p=0.07$) are often not reproducible. Further, Ioannidis (b) teaches that financial interest of investigators allows for bias and prejudices outcomes (0698, 2nd column).

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the association studies, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response asserts that the instant claims are enabled as the specification teaches only subjects with RA or sporadic RA were homozygous for the presence of a

gene encoding SEQ ID NO 1 and quotes a previous characterization provided by the examiner in the first action of 11/16/2006 and when the claims were merely drawn to the detection of a mutation in the gene. The response further asserts the teachings of the declaration of September 11, 2007 demonstrate a statistical trend toward significance with a p value of 0.07. These arguments have been thoroughly reviewed but are not considered persuasive as the specification nor declaration provide that the artisan could predictably determine the possibility of onset of RA at the art accepted level of a P value of 0.05 or less as described by Ioannidis (b). It is further noted that that the teachings of Ioannidis (b) suggest this as a starting point, but does not view this as indicative of diagnostic. Further as noted above the large variation in the occurrence of the homozygous insertion between the declaration and specification suggest there is some selection of subjects present in one of the studies as the artisan would not view one study in which a homozygous genotype was found in less than 1% of the population studied commensurate with a study in which 24% of the population studied were homozygous for the genotype.

The response continues by asserting that the claims are directed to evaluating the onset or possibility of onset of RA in human subjects and the present invention can be used in conjunction with other diagnostic methods for determining a subject propensity for developing RA. These arguments have been thoroughly reviewed but are not considered persuasive as the claims while reciting open language allowing for the inclusion of additional steps do not present such a limitation, nor does the specification appear to support the use of additional diagnostic steps. Thus it would be

unpredictable to practice the invention as claimed without a statistical correlation in a large population without additional diagnostic steps to determine the possibility of onset of RA in human subjects by the presence of homozygous insertion as taught by the art of record.

The response further asserts that Hirschhorn and Ioannidis (a) do not present any reason to contend the predictability of the instant invention. This argument has been thoroughly reviewed but is not considered persuasive as Hirschhorn and Ioannidis (a) teach that most prior art studies associating a gene or polymorphism with a disease are not reproducible and thus not predictable. Further as the amended rejection presented above denotes Hirschhorn specifically analyzed studies associating genes with RA and found that none of these studies were reproducible (tables 1 and Table 3). Thus Hirschhorn and Ioannidis (a) do suggest unpredictability of the instant claims in general and specifically as they are directed to RA.

The response asserts that the combination of the data from the specification and declaration demonstrate the instant claimed invention is reproducible and thus enabled. These arguments have been thoroughly reviewed but are not considered persuasive as neither the specification nor declaration demonstrates that a statistical correlation was observed with the presence of the homozygous insertion and RA. Further the data from the declaration does not replicate the data of the specification in which only subjects with RA were homozygous for the insertions, as the declaration teaches that subjects diagnosed with RA or not diagnosed with RA were homozygous for the insertion. The presence of the homozygous insertion in control subjects of the declaration in

conjunction with the lack of a statistical correlation in specification or declaration demonstrate that the presence of the homozygous insertion is not predictably associated with evaluating onset or the possibility of onset of RA by standards of the art.

The response traverses the observations of previous office actions made based on the differences in the data presented in the specification and declaration; in which the specification teaches that only subjects with RA contained the homozygous insertion and this was less than 1% of the population assayed, while the declaration teaches the homozygous insertion was found in 24% of the subjects studied and nearly a third of the subjects in the declaration that were homozygous for the insertion but did not have RA. These arguments have been thoroughly reviewed but are not considered persuasive as the discrepancies in the rate of occurrence would bring to question the populations studied as addressed above, and suggest unpredictability based on sample size, etc as addressed by Ioannidis (b), however this by itself does not suggest the unpredictability. However, as there is great variability in the data between the specification and declaration and there is no statistical correlation of the homozygous insertion with RA in any of the art of record, and the unpredictability of association studies in general and specifically in association studies with RA as taught by Hirschhorn, the rejection is maintained as the evidence suggest unpredictability of the claimed method.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
Primary Examiner, Art Unit 1634